REMARKS

Upon entry of this amendment, Claims 276-351 constitute the pending claims in the instant application. New Claims 339-351 are added to further clarify the subject matter claimed. Support can be found throughout the specification, *see*, for example, page 24, 1st paragraph; page 54, 2nd full paragraph; page 12, last paragraph; and page 55, 2nd full paragraph. No new matter is introduced.

Applicants note that in the pending non-Final Office Action, the Examiner has advanced a new ground of enablement rejection never before advanced during the seven-plus-year prosecution of the instant application despite prior presentation of claims of similar or broader scope. Pursuant to MPEP 707.07(g), "[p]iecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references. (*See* MPEP § 904.03.) Major technical rejections on grounds such as lack of proper disclosure, lack of enablement, serious indefiniteness and *res judicata* should be applied where appropriate even though there may be a seemingly sufficient rejection on the basis of prior art." Applicants do understand that this is the first examination of the subject application by the present Examiner; however, Applicants would still appreciate the Examiner's confirmation that the pending claims have been fully and completely examined at this time.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim Rejections under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 276-281, 283-321, and 323 are rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for a method of treating an oncological disease comprising administering to a host a complex formed from CA 125 and the monoclonal antibody B43.13 or antigen-binding fragment thereof that binds to CA 125, and wherein the complex induces host antibodies and cytotoxic T-cells reactive with at least one other epitope of the tumor associated antigen," allegedly "does not reasonably provide enablement for the administration of any other

complex of a soluble tumor antigen and a monoclonal antibody or antigen-binding fragment thereof." The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner argues that the specification teaches the elicitation of host immune response induced by a complex comprising CA 125 and the B43.13 murine monoclonal antibody (mAb) or antigen-binding fragment thereof, but this data allegedly provides no "nexus for the use (of) antibodies which bind to alternate epitopes within CA 125, or antibodies that bind to CA 19.9, CA 15.3 and PSA." Applicants note, however, that the Examiner has acknowledged that the specification is enabling with respect to other anti-CA 125 antibodies binding the same epitope as that of B43.13 (*see*, for example, page 5, last paragraph of the August 9, 2006 Office Action). New Claims 343-345 have been added drawn to this subject matter.

Applicants also note that while the Examiner has referred to the administration of a *complex*, the pending claims are directed to methods of contacting *in vivo* selected multi-epitopic antigens with non-radiolabeled *antibody or antigen binding fragment thereof.* In other words, in the instant application, what is being administered is non-radiolabeled antibody or antigen binding fragment thereof, not an antigen-antibody complex. A complex of the multi-epitopic antigen and the administered non-radiolabeled antibody or antigen binding fragment thereof forms *in vivo*, and contributes to the elicitation of either an effective T-cell response or an effective humoral response or both. Applicants realize that this is likely an oversight on the part of the Examiner, due to the fact that claims in the co-pending application U.S.S.N. 09/152,698 are directed to methods of administering complexes, and the fact that the reasons for rejection are substantially the same in this and the co-pending application. However, clarification of the record is respectfully requested.

To support her position, the Examiner cites a passage from one of the earlier applications (WO 99/65517) to which the instant application claims priority, and asserts that:

> "...the post filing reference teaches the importance of targeting an epitope which is not a dominant epitope in order to elicit antibodies and immune recognition against subdominant epitopes and that not all murine antibodies will possess the criteria of targeting an epitope which is not a dominant human epitope. Without this

> information published in 1997 [sic], it would be undue experimentation in order to screen all possible antibodies, including antibodies from a multitude of experimental hosts and human antibodies, for the ability to evoke antibodies to a different epitope on CA 125 than that bound by the antibody or T-cell recognition of CA 125."

Applicants note that this passage is not a teaching from "post-filing date art" but rather a priority document – in fact, the exact same passage can be found on page 13, the 1st full paragraph of the instant specification.

Applicants respectfully submit that the Examiner has misunderstood the disclosure of the instant specification and that of the priority documents.

The Teaching of the Instant Specification

The instant specification teaches that contacting a multi-epitopic antigen in the host serum with a binding agent (such as an antibody or binding-fragment thereof) promotes the formation of a complex *in vivo*, leads to *increased immunogenicity* of the host multi-epitopic antigen, and the elicitation of a humoral and/or cellular response *in vivo* (*see*, for example, page 12, 5th full paragraph). There is no requirement, however, that the binding agent (*e.g.*, antibody) must bind to a non-dominant epitope of the multi-epitopic antigen in order to increase its immunogenicity or to produce the desired humoral and/or cellular response *in vivo*.

Pursuant to MPEP 2138.05, "[an] inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice." *See Parker v. Frilette*, 462 F.2d 544, 547 (CCPA 1972). Nevertheless, while not wishing to be bound by any particular theory, the instant specification does provide several potential mechanisms through which the observed stimulated host immune responses (humoral and/or cellular) may occur. *See*, for example, page 16, 3rd full paragraph, and page 32, 1st full paragraph. Specifically, in terms of the humoral response that produces antibodies, at least two mechanisms may be responsible for the observed enhanced immune responses – the Ab3 pathway (anti-anti-idiotype pathway) or the Ab1c pathway (also known as the Ab3' pathway). *See* page 32, 1st full paragraph.

Merely to illustrate, suppose there is a host antigen A (*e.g.*, CA 125), which may comprise 10 epitopes, E1 – E10, with E1 being the most dominant epitope as "seen" by the host immune

system, and E10 being the least dominant. Further suppose that there is a monoclonal antibody Mab (*e.g.*, B43.13), which binds the E3 epitope on antigen A. By administering the Mab into a host with circulating antigen A, a complex between the host antigen A and the antibody Mab is formed *in vivo*. Because the binding by Mab may have increased the immunogenicity of the host antigen A, once Mab is administered to the host to form the *in vivo* Mab / A complex, the host immune system may now recognize other epitopes on antigen A, such as E2, E5, E6, *etc.*, and generate *host* anti-A antibodies (**the Ab1c / Ab3' pathway antibodies**) against such subdominant epitopes.

Alternatively or in addition, at least when the antibody Mab is from a heterologous species, such as when the host is a human and the Mab is a mouse monoclonal antibody, the host (human) immune system may recognize the mouse antibody Mab as foreign. Thus *host* anti-idiotype antibodies Ab2β may be generated. Such Ab2β antibodies in turn trigger the production of *host* anti-anti-idiotype antibodies Ab3 (**the Ab3 pathway antibodies**), which should also recognize E3 – the antigen A epitope bound by Mab.

Either way, an effective *host* antibody (humoral) response is triggered *in vivo* by injecting Mab. Similarly, a cellular response is also produced in the host. *See* page 32, 3rd full paragraph.

No Undue Experimentation is Necessary

According to the teaching of the instant specification, binding of an antibody, for example, a heterologous antibody (*e.g.*, a murine antibody, such as B43.13), to a host antigen previously unable to elicit an effective host immune response (*e.g.*, a human antigen, such as CA 125) alters / enhances the host immune response against the antigen. As explained herein, there is no requirement for the administered antibody to recognize a non-dominant epitope on the antigen, as the Examiner suggests. Also, there is no need to perform undue experimentation in order to screen for an antibody which, when complexed with the multi-epitopic antigen, would trigger the effective host immune response.

Again, merely for the purpose of illustration, the above-referenced antigen A / antibody Mab example may also be used to make the point.

As a skilled artisan will understand, potential immune response against self-antigens

(antigen A, *e.g.*, CA 125) is eliminated or suppressed during fetal development, by deletion of T- / B-cells capable of recognizing self-antigens. Thus in humans, for example, T- / B-cells capable of recognizing the most dominant antigen A epitope (E1) may not exist. However, T- / B-cells capable of recognizing the other subdominant A epitopes, such as E2-E10, may exist (but are suppressed). As a result, a host may not be able to mount an effective immune response (humoral or cellular) against cancer cells bearing antigen A. This is consistent with the Madiyalakan teaching in WO 99/65517 that it may be important to stimulate T-cell response against the subdominant self-epitopes (such as E2-E10) to eliminate cancer cells.

However, this disclosure does not mean that one must first select a specific subdominant epitope (such as E3, which in this hypothetical example is recognized by antibody Mab) in order to produce an antibody that can elicit the desired host immune response. Rather, in view of the teaching of the instant specification, a skilled artisan can readily envision that other antibodies, *e.g.*, those specifically binding to the E1, E2, E4, ..., or E10 epitopes, can also be used to form *in vivo* complexes with the selected host serum antigen A.

In the hypothetical example above, Mab happens to bind E3, which is not the most dominant antigen A epitope as the host immune system "sees" and responds to the antigen. As a result, the A / Mab *complex* becomes more immunogenic compared to antigen A alone as an antigen. Without wishing to be bound by any particular theory, this may be because: (1) the complex is more efficiently taken up by the professional APC (Antigen Presenting Cells), (2) the antibody Mab is acting like an immune-stimulating adjuvant, (3) "[e]pitopes of the antigen are blocked by the complexing antibody and are either protected from processing or processed at different sequences, thus creating new peptides for MHC-binding," and/or (4) new antigen A epitopes are exposed due to conformational changes induced by Mab binding (*see* page 49, 1st full paragraph of the instant specification). It is also possible that the antibody (*e.g.*, Mab) targets the complex to the Fc receptors on dendritic cells for more efficient processing.

As a result, host antibodies against antigen A may be produced through either the Ab3 pathway or the Ab1c pathway, or both. Like Mab, the Ab3 pathway host antibodies also recognize E3. In contrast, the Ab1c pathway antibodies may recognize E2 or any of E4-E10. Anti-E1

antibodies may not be present, because host B-cells against E1 are likely deleted during fetal development.

Similarly, a cellular immune response against antigen A-bearing cells may also be elicited.

Moreover, there is no requirement that Mab must bind to a subdominant epitope (such as E3 in this example). There is no obvious reason why the claimed methods will be non-functional if Mab happens to recognize E1, the most dominant antigen A epitope. Specifically, if Mab is produced in a mouse against a *human* (foreign) antigen A, there is no clonal deletion of mouse B-cells immunoreactive with the most dominant *human* A epitope E1. Thus Mab could well bind the most dominant antigen A epitope E1. When the heterologous Mab is injected into a host to form the Mab / A complex, host Ab1c antibodies and/or Ab3 antibodies may be generated, with the host Ab1c antibodies recognizing (some or all of) E2-E10 of antigen A, and the host Ab3 antibodies recognizing E1 of antigen A. Even if no Ab3 antibodies are produced, the host Ab1c antibodies are still sufficient to provide an effective host anti-antigen A immune response.

Either way, a skilled artisan need not perform undue experimentation "to screen all possible antibodies, including antibodies from a multitude of experimental hosts and human antibodies," as the Office Action suggests, in order to identify other antibodies capable of resulting in elicitation of effective host immune response. A skilled artisan can readily carry out at most routine experimentation to produce new antigen-specific antibodies, or simply use existing antigen-specific antibodies in the subject methods. A skilled artisan can also carry out at most routine experimentation, such as using art-recognized functional assays, to verify that the identified antigen-specific antibodies are capable of forming *in vivo* complexes with the serum antigens, and/or eliciting the desired humoral or cellular immune responses. A skilled artisan would appreciate that screening for such complexes and functions, if necessary, involves no more than routine experimentation, certainly no more than the amount of routine experimentation required to screen a hybridoma library for hybridoma clones producing a desired monoclonal antibody.

Experimental Support in the Specification

The Examiner asserts that "[t]he specification does not provide any guidance for the selection of a different antibody which binds to CA 125, nor of antibodies which bind to epitopes of

CA 125 that differ from the epitope bound by Mab 43.13." Applicants respectfully disagree.

The instant application discloses multiple working examples. For example, Figure 4 of the instant application explicitly discloses that two *different* anti-CA 125 antibodies, *i.e.*, B43.13 and B27.1, each recognizing a *different CA 125 epitope* (*see* page 48, lines 17-18 of the specification), can both form an antibody / CA 125 complex that stimulates immune response (*see* Figure 4 legend on page 15). In contrast, as a negative control, an isotype-matched control antibody MOPC-21 was ineffective (Figure 4).

Since antibody B27.1 recognizes a CA 125 epitope distinct from that recognized by antibody B43.13, the data in the specification demonstrates that at least the two tested, different anti-CA 125 antibodies can both induce the desired immune responses.

Furthermore, Applicants submit herewith a Rule 132 Declaration (with **Exhibit A**) by inventor Birgit C. Schultes, Ph.D., which Declaration provides additional data showing that a third monoclonal antibody – AR9.6 – which recognizes yet another CA 125 epitope distinct from that recognized by B43.13, also strongly stimulates T-cell response against CA 125 when dendritic cells present the AR9.6 – CA 125 complex to naive T-cells.

According to the Declaration, two different CA 125 complexes with two different anti-CA 125 monoclonal antibodies (*i.e.*, B43.13 and AR9.6) were tested for their abilities to stimulate human T-cell activation, as measured by two independent T-cell activation assays, the Intracellular Cytokine (ICC) staining assay for IFN-γ, and the CTL assay on CA 125-bearing cancer cell line NIH:OVCAR-3. Specifically, human peripheral blood leukocytes (PBLs) were first purified from three HLA-matched healthy donors. From these purified PBLs, about 70-85% pure human monocytes and about 80-90% pure human T-cells were then separately generated by negative selection. The purified monocytes were then used to generate immature dendritic cells (immature DCs) by culturing the monocytes in GM-CSF and IL-4. The resulting immature DCs were loaded with two different antigen-antibody complexes, namely the B43.13 / CA 125 complex and the AR9.6 / CA 125 complex, and were further matured with TNF-α and IFN-α and used to stimulate the purified T-cells. As controls, immature DCs were also loaded with either CA 125 alone, B43.13 alone, AR9.6 alone, or medium (as a negative control), and these control loaded immature DCs

were matured similarly, and used similarly for T-cell stimulation. The results clearly indicate that, in both the CTL assay and the ICC assay, both the B43.13 / CA 125 complex and the AR9.6 / CA 125 complex significantly stimulated T-cell activation compared to either antibody alone, antigen alone, or the negative control (media alone).

These experiments further demonstrate that no undue experimentation is necessary to practice the full scope of the claimed invention.

Furthermore, the Office Action explicitly admits that the instant specification provides several working examples regarding the use of antibodies against the other recited antigens (*e.g.*, CA 19.9, CA 15.3, and PSA). *See* the paragraph bridging pages 6 and 7 of the Office Action.

In summary, the instant specification has provided at least two working examples (including but not limited to the mouse monoclonal antibody B43.13) falling within the scope of the claimed method to show that antibodies or antigen-binding fragments thereof alter or enhance the host immune response against several host antigens (*e.g.*, CA 125) previously unable to elicit effective host immune responses. Further experiments in the Rule 132 Declaration submitted herewith provide additional working examples using yet another anti-CA 125 monoclonal antibody AR9.6. Thus, all pending claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

The Office Action also asserts that "neither the specification nor the art teaches how to expose subdominant epitopes on soluble tumor antigens that will be effective to treat an oncological disease," although the Office Action also states that "[i]t is noted that the administration of the antigen antibody complex can result in the priming of the immune response to subdominant epitopes of the soluble tumor antigen which are not accessible on the tumor surface by virtue of the conformation of said tumor antigen while part of the tumor surface."

If the Examiner is concerned about the accessibility of one or more subdominant epitopes on a multi-epitope tumor antigen, Applicants submit that most multi-epitope antigens (such as CA 125, MUC-1, CA 19.9, *etc.*) are large, and can simultaneously bind at least two and most often numerous

binding agents, as demonstrated by sandwich immunoassays that are used in routine laboratory determinations of the presence and quantity of antigens. The binding agent pairs may target the same or different sites in these determinations. For example, the original commercial assays for CA 19.9 and CA 125 were homogeneous sandwiches. The TRUQUANT™ OV2 test for determining CA 125 levels used a combination of B43.13 and B27.1 anti-CA 125 antibodies (*see* **Exhibit B** herewith), while the second generation CA 125 II™ diagnostics test (Fujirebio Diagnostics, Inc., Malvern, PA) uses a combination of M11 and OC 125 anti-CA 125 antibodies (*see* CA 125 II™ diagnostics test marketing material submitted herewith as **Exhibit C**).

The lack of host immune response toward such antigens may not be the result of epitope inaccessibility (as the Office Action suggests), but rather the result of immune tolerance (*e.g.*, the host immune system is coaxed *not* to mount an immune response against the *accessible* subdominant epitopes). The instant specification teaches several potential mechanisms by which complex formation *in vivo* may break the immune tolerance (*see* above in page 16 of the instant response), although the precise mechanism is unclear.

However, if Applicants' above understanding of the Examiner's concern is incorrect, Applicants respectfully request clarification from the Examiner.

The Office Action, while acknowledging that the specification provides several working examples regarding the use of antibodies against the other recited antigens (*e.g.,* CA 19.9, CA 15.3, and PSA), alleges that the examples "fail to provide a nexus for the induction of an effective anti-tumor response in a patient with a naturally occurring tumor, or the induction of an effective anti-tumor response in a human patient." To support this position, the Office Action cites a few references stressing the general difficulty in extrapolating animal data to clinical results.

However, such general difficulties exist in almost all cases without direct human clinical data. If no animal model can be useful, the Office Action is essentially requiring nothing short of human clinical data to demonstrate the enablement or effectiveness of the claimed invention.

Applicants submit that such a strict requirement is inconsistent with the relevant case law requiring merely a "reasonable" correlation of the *in vitro* or *in vivo* animal working examples with the claimed method.

Pursuant to MPEP 2164.02:

> "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. ... if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> ...
>
> A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
>
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Applicants submit that the animal models provided in the specification bear such a *reasonable* correlation to the claimed methods, in that they each represent the closest possible animal model short of actual human clinical trial. In some examples, *human* immune system cells are used to reconstitute the immune-deficient SCID mouse, and *human* cancer cells are used as target cells in these experiments. *See*, for example, Examples 3 and 6.

In summary, the instant specification has provided multiple working examples falling within the scope of the claims to show that antibodies or antigen-binding fragments thereof alter or enhance the host immune response against CA 125 and several other host antigens. Thus, all pending claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, First Paragraph – Biological Deposit

Claims 286, 287, 292, 306, 307, 312, 326, 327, and 332 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action asserts that the specification fails to teach or provide complete evidence either that the claimed antibodies are known and readily available to the public, or complete evidence of the deposit of the antibodies. The Office Action argues that, to practice the methods of Claims 286, 287, 292, 306, 307, 312, 326, 327, and 332, a skilled artisan must have possession of the exact claimed antibodies.

The mouse hybridoma B43.13 (MCB-ALT-96), which produces the antibody B43.13, was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209, on May 18, 2000, and was given ATCC deposit number PTA-1883.

The mouse hybridoma AR44.6R1331, which produces the antibody Alt-3, was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209, on November 17, 2000, and was given ATCC deposit number PTA-2691.

The mouse hybridoma AR18.4R3313, which produces the antibody Alt-4, was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209, on November 17, 2000, and was given ATCC deposit number PTA-2692.

The mouse hybridoma AR47.47, which produces the antibody AR47.47, was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209, on April 29, 1998, and was given ATCC deposit number HB-12526.

Applicants' attorney hereby states that the deposits have been accepted by an International Depository authority - the American Type Culture Collection (ATCC) - under the provisions of the Budapest Treaty, and that upon the grant of a patent on this application with claims referencing the deposited hybridomas, all restrictions upon public access to the deposits will be irrevocably removed, and that the deposits will be maintained for the required time and replaced if viable samples cannot be dispensed by the depository if required.

Enclosed as **Exhibits D – F** are copies of the deposit receipts from the American Type Culture Collection (ATCC).

Furthermore, Applicants have amended the specification to recite the date of deposit and the complete name and address of the depository. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner has also indicated, *inter alia*, that, if the deposits were made after the effective filing date of the application for patent, "a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing identical monoclonal antibodies as described in the specification and were in the applicant's possession at the time the application was filed."

Applicants hereby submit a copy of a verified statement from inventor Birgit C. Schultes, Ph.D., to satisfy the requirement under 37 C.F.R. § 1.804(b). Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting Rejections

Claims 276-282, 299-302, 313-315, 319, 334, and 335 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 30, 71, 76, 85-88, 96, 98-100, 103-114, 117-119, and 123-128 of co-pending U.S. Application No. 09/152,698.

Applicants submit that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

If the allegedly conflicting claims are first allowed in the co-pending U.S. Application 09/152,698 and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R.

§ 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, as appropriate, upon indication of allowable subject matter.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response other than the fees submitted concurrently. However, if an additional fee is due, please charge our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **AREX-P03-004**.

Dated: February 8, 2007

Respectfully submitted,

By_____

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